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ART UNIT	**PAPER NUMBER**
1632	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/782,129	HADLACZKY ET AL.	
	Examiner	Art Unit	
	Anoop Singh	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1-22 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 1-22 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☒ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date 5/21/04; 7/30/04; 9/17/04; 10/21/04; 6/16/05; 9/28/05; 11/18/05; 3/31/06; 5/25/06
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Applicants submission of substitute specification and abstract filed on August 4, 2004, has been received and entered. Claims 1-22 are pending.

Claims 1-22 are under consideration.

Title

A new title is required that is clearly indicative of the invention commensurate in scope with claim. Appropriate correction is required.

Priority

Applicant's claim for the benefit of a prior-filed application under 35 U.S.C. 119(e) or under 35 U.S.C. 120, 121, or 365(c) is acknowledged. Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 120 as follows:

The later-filed application must be an application for a patent for an invention, which is also disclosed, in the prior application (the parent or original nonprovisional application or provisional application). The disclosure of the invention in the parent application and in the later-filed application must be sufficient to comply with the requirements of the first paragraph of 35 U.S.C. 112. See *Transco Products, Inc. v. Performance Contracting, Inc.*, 38 F.3d 551, 32 USPQ2d 1077 (Fed. Cir. 1994).

The disclosure of the prior-filed application, Application No. 09/096648 now US Patent 6743967, fails to provide adequate support or enablement in the manner provided by the first paragraph of 35 U.S.C. 112 for one or more claims of this application. In the instant case, claim 1, 8 and 11 are directed to a method that requires introducing "a cell" comprising SATAC, however the only support provided in the specification consistent with making an animal is using a zygote/embryo or stem cell. It is noted that claims 32 and 34 in parent application '648 is directed to a method that requires introducing a satellite artificial chromosome into an embryonic cell subsequently limiting to an embryo. Hence, it is apparent that introducing any cell comprising SATAC would broaden the scope of instant invention. Accordingly, priority for instant claims 1-3, 7-11 will be 2/18/2004.

Oath/Declaration

The oath or declaration is defective. A new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application by application number and filing date is required. See MPEP §§ 602.01 and 602.02. The oath or declaration is defective because: Instant oath relates this application as continuation of application number 09/096648, now US Patent number 6743967. However, this application presents a claim for subject matter not originally claimed or embraced in the statement of the invention in application number 09/096648. Furthermore, the disclosure of the prior-filed application, Application No. 09/096648, fails to provide adequate support or enablement in the manner provided by the first paragraph of 35 U.S.C. 112 for one or more claims of

this application. Claims are directed to a method that requires introducing "a cell" comprising SATAC, however the only support provided in the specification consistent with making an animal is using a zygote/embryo or stem cell. Hence, as discussed above introducing a cell comprising SATAC would broaden the scope of instant invention. Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-22 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for producing a transgenic mouse comprising: microinjecting satellite artificial chromosome (SATAC) into cells selected from a list consisting of zygote, fertilized ovum; implanting said cells comprising SATAC in female mouse, wherein said cell develop into an embryo in a female mouse and allowing said embryo to develop into a transgenic mouse comprising the SATAC; and methods for producing a transgenic mouse, comprising introducing a mouse ES cell comprising a mammalian SATAC into a mouse embryo, introducing said embryo into a female mouse and allowing the embryo to develop into a transgenic mouse comprising said SATAC, does not reasonably provide enablement for methods for producing transgenic non-human mammal by introducing a cell comprising a SATAC, wherein the

cell develops into an embryo in a female nonhuman mammal or using any other ES cell to make any other nonhuman transgenic animal. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

In determining whether Applicant's claims are enabled, it must be found that one of skill in the art at the time of invention by applicant would not have had to perform "undue experimentation" to make and/or use the invention claimed. Such a determination is not a simple factual consideration, but is a conclusion reached by weighing at least eight factors as set forth in In re Wands, 858 F.2d at 737, 8 USPQ 1400, 2d at 1404. Such factors are: (1) The breadth of the claims; (2) The nature of the invention; (3) The state of the art; (4) The level of one of ordinary skill in the art; (5) The level of predictability in the art; (6) The amount of direction and guidance provided by Applicant; (7) The existence of working examples; and (8) The quantity of experimentation needed to make and/or use the invention.

These factors will be analyzed, in turn, to demonstrate that one of ordinary skill in the art would have had to perform "undue experimentation" to make and/or use the invention and therefore, applicant's claims are not enabled.

Furthermore, USPTO does not have laboratory facilities to test if an invention will function as claimed when working example are not disclosed in the specification, therefore enablement issues are raised and discussed based on the state of knowledge pertinent to an art at the time of the invention, therefore, skepticism raised in enablement rejections are those raised in the art by artisan of expertise.

Claims 1, 8, 14, 18 and 21 are broad in scope. The following paragraph will outline the full scope of the claims. In the instant case, claims encompass any cell comprising SATAC that is introduced in a female nonhuman animal wherein cell develops into an embryo or cell comprising SATAC that develops into a nonhuman embryo in culture. As recited instant claims would also embrace the implantation of embryos into surrogate mother of different species. Furthermore, claim 7 limits the independent claim to include any bird, mouse, reptile, amphibian, and insect or fish cell. In addition, claims19 embrace a method of making transgenic animal by introducing an embryonic stem cell comprising a SATAC into embryo and then introducing the embryo to develop into a transgenic animal and then allowing embryo to develop into a transgenic animal. It is noted that, claims 19-20 embrace embryonic stem cell (ES cell) comprising SATAC from any species introduced into a female mouse to get transgenic animal comprising SATAC, subsequently limiting animal to include bird. The disclosure provided by the applicant, in view of prior art, must encompass a wide area of knowledge to a reasonably comprehensive extent. In other word each of those, aspect considered broad must be shown to a reasonable extent so that one of the ordinary skills in the art at the time of invention by applicant would be able to practice the invention without any undue burden being on such Artisan.

As a first issue, claim 1 embraces a method for producing nonhuman animal comprising introducing a cell comprising a SATAC into a nonhuman female wherein cell develops into an embryo in a female non-human animal. The specification contemplated microinjection of megachromosomes isolated from fusion cell line in fertilized mouse

embryos or fusing megachromosome-containing cell line with mouse embryonic stem cells and then transplanted into mouse blastocysts the resultant fusion cell line comprising megachromosomes carrying the transgenes to obtain transgenic nonhuman animal (see paragraph 540 and 541 of the specification). It is noted that prior to instant invention while reviewing strategies to engineer human chromosome, Saffery et al (J Gene Med. 2002 Jan-Feb;4(1):5-13) describe problems associated with the production of useful human engineered chromosome (HEC) including size and difficult to fully characterize, especially those containing highly repetitive DNA (see page 11, column 2, lines 4-15). It is noted that Saffery et al state that "the large size of HECs also makes them difficult to manipulate in terms of the introduction of genes and the transfer from cell to cell in an intact form. Present methodologies do not readily lend themselves to delivering chromosomes of this size to in vivo cell targets" (see page 12, column 1, paragraph 1). Saffery et al describe that the specific production of a human SATAC that shows a 95% retention rate after 50 generations, demonstrating mitotic stability and persistence of b-galactosidase expression over several generations. However, Saffery et al states "SATACs produced by these procedures are typically tens to hundreds of megabases in size, contain substantial amounts of different classes of repetitive satellite DNA, and are highly complex in structure. Structural mapping and full sequence characterization of these chromosomes are likely to be impossible (see page 8, column 1, paragraph 2). Thus, the lack of control over their mode of formation produces the same drawbacks as HECs derived using de novo approaches, which does not permit control over gene copy number or the structural integrity of the genes incorporated into

the HECs (see page 8, paragraph 1, lines 101-20). In addition, in a post filing art, Irvine et al (Trends Biotechnol. 2005; 23(12): 575-83) report that "there are several different methods for the transfer of HECs between cell types but, with the exception of microcell-mediated cell transfer (MMCT), methods for transferring HECs into human somatic cells require an initial purification step to isolate HECs away from other human chromosomes and chromosome fragments" (see page 579, column 1, paragraph 2). It is apparent from the cited art that structural mapping, sequence characterization of SATAC was evolving and not resolved at the time of filing of this application. Furthermore, as recited claim 1 is not enabled commensurate with the full scope of the claim as it is clear that transferring SATAC into human somatic cells would require an initial purification step or specifically microcell-mediated cell transfer.

As a second issue, independent claim 1 requires introducing a cell comprising a satellite artificial chromosome into a female nonhuman animal wherein cell develops into an embryo while claim 8 requires cell-comprising SATAC to develop as embryo in culture. The specification contemplated several method to introduce DNA into animal cells using any known procedure, including, but not limited to direct uptake, incubation with polyethylene glycol (PEG), microinjection, electroporation, lipofection, cell fusion, microcell fusion, particle bombardment, including microprojectile bombardment (see paragraph 137 of the specification). However, the specification does not teach how to make or use any nonhuman transgenic animals other then transgenic mouse comprising SATAC made by these methods. It is noted that instantly claimed invention recite every possible method of DNA introduction in a cell and every possible cell type

as embryo as source wherein the embryo is developed *in vitro* or *in vivo*, however, the specification does not provide any specific guidance as to how the method would be carried out using any cells. In addition, claim 11 as written limits the method of claim 1 to include SATAC is isolated prior to introducing into cell that is transferred into a female nonhuman animal. Given the broadest reasonable interpretation, as recited these cells would also encompass introducing a SATAC in any cell including somatic cell and using any other method such as transferring the nucleus of the cell into any enucleated recipient cell and transferring recipient cell into a maternal nonhuman animal. The state of art summarized by the references of Wolf et al (Journal of Biotechnology 65: 99-110, 1998); Stice et al (Therigeneology, 1998, 49: 129-138); Yanagimach et al (Molecular and Cellular Endocrinology, 2002, 187, 241-248); Oback and Wells (Cloning and Stem Cells, 2002, 4, 169-174, IDS) and Kuhholzer and Prather (The Society for Experimental Biology and Medicine, 2000, 224: 240-245, IDS) disclose limitation of routine method of nuclear transfer. For instance, Wolf et al emphasize several factors that influence embryo cloning by NT, such as the state of development and cell cycle of the donor cells, the choice of recipient cell, the method of activation of oocyte. The specification does not provide any guidance to these parameters (see entire article). Stice et al reported timing of embryonic genome activation might be partly responsible for species-specific differences. Stice et al further noted that method used for cloning sheep where the donor cell was in G0 could not be used in other animal species (see the last paragraph on page 131). This clearly suggests that method used in one animal or species could not be used in another animal or species, the specification does not

provide any guidance how claimed method would be practiced. Yanagimachi et al state that "perhaps no single protocol for cloning that works for all mammalian species, because, the characteristics of an oocyte and donor cells are from species to species. A protocol that is best for a given species may not be suitable for another species. Technical details must be worked out for each species". It is emphasized that applicants have provided no guidance in this regard. In summary, the specification as filed is not enabling for the claimed invention because the state of the art of producing transgenic animal from any donor cell into any recipient cell and transfer of SATAC in a cell that develops into embryo in a female nonhuman animal was not predictable and an artisan would have required extensive experimentation to practice the claimed invention and such experimentation would have been undue since the experimentation was not routine, and the state of the art was unpredictable and the specification did not teach how to address the limitation and unpredictable nature of the invention.

As a third issue, the specification does not provide any evidence to support that STATC could be introduced and expressed at an optimal level such that it could be used for its intended use. The specification contemplated these to be used for expressing heterologous genes such as CFTR. The specification further teaches that one could introduce such sequences into SATACS by site-specific integration (see paragraph 161 of the specification). However, specification does not teach how to accomplish such a homologous recombination. In particular, although the specification teaches how to generate specific SATAC, it does not teach how to generate SATAC that contain and express heterologous genes, how to introduce into embryos or ES

cells, or how to generate transgenic nonhuman animals which express heterologous genes at a high enough level to be useful. The prior art suggest unpredictability associated with such an integration. Prior to instant invention, Brown et al (Curr Opin Genet Dev. 1996 Jun 1; 6(3): 281-8, IDS and Brown et al Trends in Biotechnology, 18, 218-223, IDS) teach that frequency of recombination in mammalian somatic cell is too low to allow for such manipulation and that mammalian artificial chromosome would have to be shuttled into alternative cellular host (see page 282, column 2, paragraph 3 to page 283). However, whether these chromosome vectors could be transmitted to next generation through the germline transmission, a crucial issue for potential utility of this procedure remains unpredictable for most of the species. It is art recognized that possibility of an extra chromosome might inhibit the differentiation of ES cell into functional germ cell leading to sterility of sterility in some chimaeras. These observations are supported by Brown, who addresses the requirement for mini-chromosomes to pass through meiosis. Brown states that male meioses are more sensitive to the presence of unpaired chromosomes than female meioses and an unpaired marker chromosome will often block male meiosis during the first division. Brown further describes that the presence of the mini-chromosome in the germline of a male, might render that animal infertile. Brown evince a positive outlook for introducing the mini-chromosomes in pairs into the germline of either males or females through ES cells since most ES cell lines are 40,XY and have the favorable characteristic of tending to masculinise the germline of a female host. However, this approach may, require homologous mini-chromosomes that are selectable with at least two markers. Brown et

al emphasize that the size and sequence requirements for pairing and exchange in mice, however, have not been established and therefore it is unclear whether this approach will work (see page 287, column 1, paragraph 1). The cited art clearly suggest technology for transmission of human chromosome fragment comprising heterologous gene to produce transgenic nonhuman animal except mouse was not routine rather had problems at the time of filing of this application as stated in this office action.

As a fourth issue, the specification does not disclose whether SATAC would be maintained stably in the any transgenic nonhuman animal. Although, Co et al (Chromosome Research, 2000, 8, 183-191, IDS) disclose transgenic mice and germline transmission of a murine SATAC introduced into embryo by pronuclear microinjection, the art does not provide any guidance regarding any other transfer method or nuclear transfer as broadly contemplated by the instant claims 1. While the art teaches that SATAC are stable, the introduction of a SATAC containing a heterologous gene large DNA such as CFTR in a donor cell or use of a donor cell in producing transgenic nonhuman animal will be unpredictable as stated earlier in this office action (supra). Furthermore, it would be unpredictable whether SATAC of different origin would function in different species as contemplated by instant invention, given the unpredictability in maintaining chromosome in the germline (Brown et al, supra). In addition, claims 1-12, 14-16, 18-20 as recited encompasses the embryos into surrogate mother of different species or any cell comprising SATAC that develops in culture into a nonhuman animal embryo. However, as stated before cell comprising SATAC could be interpreted by NT, which is not enabled (supra). It is emphasized that although, interspecies chimaerism

between few species have recently been shown, however, neither specification nor art of record show that SATAC or other artificial chromosome could be stably maintained in germ line in any chimaeric animal. In addition, McGovern (Br Vet J. 1976 Jan-Feb; 132(1): 68-75) attribute interspecies pregnancies, placental abnormalities to maternal immunological reaction against foreign antigen of the conceptus leading to immediate abortion (see the entire article). It is noted that neither specification nor art of record provide any evidence to support that cell comprising SATAC from other species would not cause immediate abortion. Because of the art, as shown above, does not disclose how to make and use the invention, the Artisan could not predict, in the absence of evidence to the contrary, that such a method as Applicant claims would result in a chimaeric animal, An artisan would have to carry out extensive experimentation to make use of the invention, and such experimentation would have been undue because of unpredictabilities in getting germline transmission in chimaeric animal comprising SATAC.

As a fifth issue, Prior to instant invention, the art teaches that the art of making a transgenic nonhuman animal with any specific phenotype in one species cannot be predictive of same phenotype in another or interspecies nonhuman animal. It is emphasized that in spite of great advances that have occurred in transgenic technology, the state of the art of generating transgenic animals is such that the resulting phenotype in different species would not be predictable. This is because the art of transgenic animals has for many years stated that the unpredictability lies with the site or sites of integration of the transgene into the target genome. Transgenic animals are regarded

to have within their cells cellular mechanisms which prevent expression of the transgene, such that DNA methylation or deletion from the genome (Kappell et al Current Opinions in Biotechnology 3, p. 549, col 2, par 2, 1992). Mullins et al states that not all animals express a transgene sufficiently to provide a model for a disease as the integration of a transgene into different species of animal has been reported to give divergent phenotypes (Mullins et al Hypertension 22:631, col 1, par 1, lines 14-17, 1993). While the intent is not to say transgenic animals of a particular phenotype can never be made, the intent is to provide art taught reasoning as to why the instant claims are not enabled for producing nonhuman animal. Given such differences in the expression of a transgene, particularly when taken with the lack of guidance in the specification for introducing any cell comprising SATAC that develops in embryo to make any transgenic nonhuman animal, it would have required undue experimentation to the levels of the transgene product, the consequences of that product, and therefore, the resulting phenotype. The specification fails to provide teachings or specific guidance to overcome the above described unpredictabilities, in order to successfully carry out the claimed methods of producing nonhuman transgenic nonhuman animal with a specific phenotype, and as such, the claims are not enabled commensurated with full scope of the claim.

As a sixth issue, claims 19-20 embrace a method that is directed for producing transgenic animal by introducing a cell or embryonic stem cells. ES cell from any species comprising SATAC into embryo allowing the embryo to develop into transgenic animal comprising SATAC, subsequently limiting the animal to include a bird. The art at

the time of filing further held that transgenic technology was not predictable for any species other than mouse. Since the specification discloses using mouse ES cells to produce transgenic mice via homologous recombination of targeting vectors in the ES cells, ES cells from various species are required to produce various vertebrates. However, Houdebine, 1994 (Journal of Biotechnology, Vol., 34, pp 269-287) describes that although ES cells can be used to generate transgenic animals, but this approach remains restricted to mice, ES cells from other species are not presently available (pp 279). Furthermore Mullin et al also point that non-mouse ES cell capable of providing germ line chimeras were not available (Mullins et al., Journal of Clinical Investigation, 1996, pp 1557, 1st paragraph). Campbell and Wilmut (1997, Therigenology) acknowledges report of ES-like cells in number of species, but also emphasize that there are no report of any cell line that contribute to germ line in any species other than mouse (pp 65; 2nd paragraph). Thus, the state of the art is such that ES cell technology is generally limited to the mouse system and that only putative ES cells exist for other species (Moreadith et al., J. Mol. Med., 1997 p214, abstract). In fact, even after filing of instant application, Hochepied et al (Stem Cells, 2004, 22: 441-447) state "transmission of the genotype to the offspring of chimeras has only been achieved with mouse ES cells (pp 444, right column, lines 1-3). Therefore, at the time of filing of this application, nonhuman animal could not be accomplished for any species other than mouse. The specification fails to provide sufficient guidance to make nonhuman transgenic other than mice by teaching obtaining ES cells in species other than mice. The specification

does not teach how to make nonhuman animal for any other species other than mice or correlate making mice to making transgenic for any other species.

As a final issue, claims 19-20 are directed to a method of producing any transgenic animal subsequently limiting animal to include a bird by introducing any ES cell comprising SATAC into an embryo and introducing the embryo into a female mouse and allowing embryo to develop into any transgenic animal. As recited these claims are not consistent with the specification and would encompass making transgenic bird or any other transgenic animal by introducing any ES cell comprising SATAC into embryo and introducing said embryo into a mouse to get transgenic bird. As stated earlier art of record show ES cell were generally restricted to mouse and ES cell from other species were not available at the time of filing of this application (supra). In addition, neither specification nor art of record suggest that a bird embryo would be viable in female mouse to produce transgenic bird.

In conclusion, the specification as filed in not enabling for the claimed invention commensurated with the full scope of the claim because state of the art of producing transgenic animal from any cell or any ES cell comprising SATAC into a nonhuman female animal was not predictable and an artisan of skill would have required extensive experimentation to practice the claimed invention and such experimentation would have been undue since experimentation was not routine and the state of art was unpredictable. The specification did not teach how to address the limitations and unpredictable nature of the invention commensurated with full scope of the invention.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 1, 2, 8 and 11 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1 and 8 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. In the instant case, claims require introducing cell-comprising SATAC. The claims are missing the critical steps depending on the source of the cell and method of introducing SATAC in the cell. As recited these methods require cells that are subject to different interpretation. Appropriate correction is required.

Claim 2 is vague and indefinite because of recitation of term "therapeutic product". It is not apparent from the specification what is included or excluded by this DNA encoding therapeutic product. Since it has subject to different interpretation depending on Artisan, the meets and bound of the claimed invention cannot be determined. Appropriate correction is required.

Claim 8 is vague and renders the claims infinite because as recited step (i) encompass introducing a SATAC into a cell that develops in a nonhuman embryo in

culture. It is unclear what does culture provide in step (ii) to a cell that is already developed as an nonhuman embryo. Appropriate correction is required.

Claim 11 recites the limitation "wherein the satellite artificial chromosome is isolated" in claim 11. There is insufficient antecedent basis for this limitation in the claim since claim 1 only recites two steps (i) introducing a cell comprising a SATAC and (ii) allowing embryo to develop. Appropriate correction is required.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-7, 12-21 are rejected under 35 U.S.C. 102(b) as being anticipated by Montoliu et al (Reprod Fertil Dev. 1994; 6(5): 577-84) as evidenced by Schedl et al (Nucleic Acids Res. 1992 Jun 25; 20(12): 3073-7).

It is noted that the method disclosed in the instant invention does not require that SATAC is maintained extra chromosomally, rather method only requires inserting SATAC. Prior to instant invention, Montoliu et al taught successful generation of transgenic mice harboring yeast artificial chromosomes (YACs). Montoliu et al taught different methods to show consistent expression of the transgene carried on YAC DNA. It is noted that Montoliu compared different techniques for obtaining transgenic mice carrying YACs using a 250-kb YAC bearing the mouse tyrosinase gene including microinjection of YAC DNA into pronuclei of fertilized mouse oocytes and lipofection of

YAC DNA into ES cells. Montoliu et al demonstrate that the delivery of large genomic regions covering a gene of interest is feasible (see abstract). This is further evidenced by studies disclosed by Schedl et al (Nucleic Acids Res. 1992 Jun 25; 20(12): 3073-7) that teach a method of making transgenic mice with YACs by pronuclear injection of a small YAC carrying a gene encoding tyrosinase (see abstract and). It is emphasized that since claims as recited requires inserting of SATAC into cells and do not require that it is maintained extra chromosomally. Accordingly, a method of producing a nonhuman animal comprising inserting a cell comprising YAC/BAC, wherein cell develops in an embryo and allowing embryo to develop into a transgenic nonhuman animal as taught by Montoliu et al would anticipate the claimed invention.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-22 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-20 of U.S. Patent No. 6743967.

Although the conflicting claims are not the same, they are not patentably distinct from each other because both sets of claims encompass a method for producing a transgenic nonhuman animal comprising introducing a cell comprising SATAC into a female nonhuman animal, wherein cell develops in to an embryo and then allowing the embryo to develop into a transgenic nonhuman animal. For example, Claim 1 is drawn to a method for producing a transgenic non-human animal, comprising: introducing a cell comprising a SATAC into a female non-human animal, wherein the cell develops into an embryo in a female non-human animal; and allowing the embryo to develop into a transgenic non-human animal comprising a satellite artificial chromosome. Claim 2 limits the SATAC to include a heterologous DNA that encodes a therapeutic product, subsequently limiting cell of claim 1 to include a zygote, fertilized ovum, an ovum that develops into an embryo. Claim 7 limits the cell to include a bird, mouse, reptile, amphibian, and insect or fish cell. Claim 8 is a method of producing a transgenic non-human animal embryo, comprising introducing SATAC in a cell to develop in embryo in culture. Subsequent claims limit cell to include a fertilized oocyte, an ovum, a fertilized ovum or a zygote. Claim I0 limit the method of claim 8 to include the cell that is a bird, mouse, reptile, amphibian, insect, or fish cell. Claim 11 further limit the method of claim 1, wherein the satellite artificial chromosome is isolated prior to introduction into the cell.

Claim 12 limits the method of claim 1, wherein the satellite artificial chromosome is introduced into the cell by a plurality of methods. Claim 13 limits the method of claim 1, wherein the embryo and the female non-human animal are of the same species. Claim 14 is a method for producing a transgenic non-human animal, comprising: introducing an embryo comprising a SATAC into a female non-human animal; and allowing the embryo to develop into a transgenic non-human animal comprising a satellite artificial chromosome. Claims 15-17 limit the method of 14 to include plurality of cell type, method of introducing SATAC. Claim 17 limits the method of claim 15 wherein the embryo and the female non-human animal are of the same species. Claim 18 is a method for producing a transgenic non-human animal comprising introducing a fertilized oocyte comprising SATAC into a female non-human animal. While claims19-20 are directed to a method for producing a transgenic animal using introducing an embryonic stem cell subsequently limiting animal to include a bird. Claim 21 and 22 are directed to a method for producing a transgenic non-human animal, comprising introducing an ovum comprising SATAC into a female non-human animal wherein the satellite artificial chromosome is a megachromosome derived from a cell line having all of the identifying characteristics of the cell line deposited under ECACC accession number 96040928 or 96040929. Whereas, claim 1 of the Patent No. 6743967 is directed to a method for producing a transgenic non-human mammal, comprising introducing a cell comprising a satellite artificial chromosome into a female non-human mammal, wherein the cell develops into an embryo in a female non-human mammal and allowing the embryo to develop into a transgenic non-human mammal comprising a satellite artificial

chromosome. The remaining claims 2-20 encompass all the limitations of instant application. Thus, claims of instant application differ only with respect to broader scope of animal, which encompass those specifically claimed in patent 6743967.

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., In re Berg, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); In re Goodman, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); In re Longi, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); In re Van Ornum, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); In re Vogel, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and In re Thorington, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

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Claims 1-7, 11-19 and 21-22 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claim 1-21 of copending Application No. 09/799,462.

Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims 1-21 of the '462 application when taken together with the teachings of the '462 specification would be used for making a chimeric animal made by method disclosed in the instant application. The '462 specification discusses making transgenic nonhuman animal using mammalian SATAC. See example 14 of the

'462 specification. Also, the '462 specification, contemplates introduction of SATAC by various means known in the art (paragraph 171-175). Therefore, claim 1-21, when read in light of the teachings of the '462 specification, would be used to a chimeric nonhuman animal by the same method as one disclosed in the instant invention. Therefore, both sets of claims embrace the production of a chimeric nonhuman animal comprising introducing a cell comprising SATAC and introducing the resulting cell into a host animal.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., In re Berg, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); In re Goodman, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); In re Longi, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); In re Van Ornum, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); In re Vogel, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and In re Thorington, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

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Claims 1-7, 11-18 and 21-22are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claim 1 of U.S. Patent

application no. 10/151, 081. Although the conflicting claims are not identical, they are not patentably distinct from each other because both sets of claims embrace neurons. The claims of the instant application embrace a method to produce nonhuman chimeric animal while claim 1 of the '081 application embraces a method comprising: introducing a mammalian artificial chromosome that comprises nucleic acid encoding a therapeutic product into a cell of a host animal, wherein the therapeutic product is expressed in the cell. It would be obvious that a nonhuman animal would be encompassed by the host animal produced by the method as recited in claim 1 of the '081 application since the specification of '081 contemplated treating producing transgenic nonhuman animal (see paragraph 6 of the specification). The '081 application also contemplated using artificial chromosomes in gene therapy, gene product production systems, production of humanized genetically transformed animal organs, production of transgenic plants and animals (non-human), including mammals, birds, fowl, fish, invertebrates, vertebrates, reptiles and insects (see paragraph 28 of the specification).

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Conclusion

No Claims allowed.

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure. Sang et al (Mechanism s of Development, 2004) 1179-1186. Sang et al show an optimistic outlook in the development of the methods of making transgenic bird but states "all methods either still have technical challenges to overcome or have limitations in their application. Manipulation of the oocyte or zygote is possible and may become more useful if it becomes possible to increase the frequency of integration of microinjected gene constructs". It is noted that Sang and a further review of the art in the area suggest despite serious cloning effort of transgenic bird carrying transgene in all somatic cell is not successful.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Anoop Singh whose telephone number is (571) 272-3306. The examiner can normally be reached on 9:00AM-5:30PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached on (571) 272- 0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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